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Office Action Dated: December 31, 2002

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Scott A. Waldman

Confirmation No.: 8378

Application No.: 09/724,983

Group Art Unit: 1642

Filing Date: November 28, 2000

Examiner: Gary B. Nickol

For: **ST RECEPTOR BINDING COMPOUNDS AND METHODS OF USING THE SAME**

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REPLY PURSUANT TO 37 CFR § 1.111

In response to the Official Action dated **December 31, 2002**, reconsideration is respectfully requested in view of the amendments and/or remarks as indicated below:

- ☒ **Amendments to the Specification** begin on page 2 of this paper.
- ☒ **Amendments to the Claims** are reflected in the listing of the claims which begins on page 7 of this paper.
- ☐ **Amendments to the Drawings** begin on page _____ of this paper and include an attached replacement sheet.
- ☒ **Remarks/Arguments** begin on page 10 of this paper.

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Amendments to the Specification:

Please replace the paragraph found at page 22, line 26 through page 23, line 5 with the following rewritten paragraph:

C₁ --Chemotherapeutics useful as active moieties which when conjugated to an ST receptor binding moiety are specifically delivered to metastasized colorectal cells are typically, small chemical entities produced by chemical synthesis. Chemotherapeutics include cytotoxic and cytostatic drugs. Chemotherapeutics may include those which have other effects on cells such as reversal of the transformed state to a differentiated state or those which inhibit cell replication. Examples of chemotherapeutics include common cytotoxic or cytostatic drugs such as for example: methotrexate (amethopterin), doxorubicin (adrimycin), daunorubicin, cytosinarabioside, etoposide, 5-fluorouracil ~~5-4 fluorouracil~~, melphalan, chlorambucil, and other nitrogen mustards (e.g. cyclophosphamide), *cis*-platinum, vindesine (and other vinca alkaloids), mitomycin and bleomycin. Other chemotherapeutics include: purothionin (barley flour oligopeptide), macromomycin. 1,4-benzoquinone derivatives and trenimon.--

Please replace the paragraph at page 35 line 7 through page 37, line 30 with the following rewritten paragraph:

C₂ --One aspect of the present invention relates to a method of treating individuals suspected of suffering from metastasized colorectal cancer. Such individuals may be treated

by administering to the individual a pharmaceutical composition that comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is a peptide. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent and the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable therapeutic agent. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the

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active moiety is a radiostable active agent selected from the group consisting of:

methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-fluorouracil 5-4 ~~fluorouracil~~, melphalan, chlorambucil, *cis*-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, *Pseudomonas* exotoxin, diphtheria toxin, *Clostridium perfringens* phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-fluorouracil 5-4 ~~fluorouracil~~, melphalan, chlorambucil, *cis*-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, *Pseudomonas* exotoxin, diphtheria toxin, *Clostridium perfringens* phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the active moiety is a radiostable active agent selected from the group consisting of:

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methotrexate, doxorubicin, daunorubicin, cytosinarabioside, *cis*-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, *Pseudomonas* exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a conjugated compound that comprises an ST receptor binding moiety and an active moiety wherein the ST receptor binding moiety is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:54 and the active moiety is a radiostable active agent selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, *cis*-platin, vindesine, mitomycin and bleomycin, alkaline phosphatase, ricin A chain, *Pseudomonas* exotoxin and diphtheria toxin. In some embodiments of the present invention, the pharmaceutical composition comprises a pharmaceutically acceptable carrier or diluent and a radiostable conjugated compound described in Example 1. The individual being treated may be diagnosed as having metastasized colorectal cancer or may be diagnosed as having localized colorectal cancer and may undergo the treatment proactively in the event that there is some metastasis as yet undetected. The pharmaceutical composition contains a therapeutically effective amount of the conjugated composition. A therapeutically effective amount is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual.--

Please replace the full paragraph on page 42, at lines 9 through 33, with the following rewritten paragraph:

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--Another aspect of the invention relates to unconjugated compositions which comprise an ST receptor binding ligand and an active agent. For example, liposomes are small vesicles composed of lipids. Drugs can be introduced into the center of these vesicles. The outer shell of these vesicles comprise an ST receptor binding ligand. *Liposomes* Volumes 1, 2 and 3 CRC Press Inc. Boca Raton FLA, which is incorporated herein by reference, disclose preparation of liposome- encapsulated active agents which include targeting agents that correspond to ST receptor ligand in the outer shell. Unconjugated compositions which comprise an ST receptor ligand in the matrix of a liposome with an active agent inside include such compositions in which the ST receptor ligand is selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NOS:5-54 and fragments and derivatives thereof and the active agent is selected from the group consisting of: methotrexate, doxorubicin, daunorubicin, cytosinarabioside, etoposide, 5-fluorouracil 5-4 ~~fluorouracil~~, melphalan, chlorambucil, *cis*-platinum, vindesine, mitomycin, bleomycin, purothionin, macromomycin, 1,4-benzoquinone derivatives, trenimon, ricin, ricin A chain, *Pseudomonas* exotoxin, diphtheria toxin, *Clostridium perfringens* phospholipase C, bovine pancreatic ribonuclease, pokeweed antiviral protein, abrin, abrin A chain, cobra venom factor, gelonin, saporin, modeccin, viscumin, volkensin, alkaline phosphatase, nitroimidazole, metronidazole and misonidazole.--

Please replace the paragraph on page 47, lines 19-20, with the following rewritten paragraph:

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--Compound 2-D6 comprises 5-fluorouracil 5-4 ~~fluorouracil~~ conjugated to SEQ ID NO:2.--